

HIV PREVENTION TRIAL NETWORK (HPTN) APPLICATION SUMMARY

**Submitted for the DAIDS/NIAID web site by Niru Sista and Sten Vermund,
abstracted from the HPTN application submitted for May 11, 2005**

This HIV Prevention Trials Network (HPTN) Leadership application responds to RFA AI-05-001, Leadership for HIV/AIDS Clinical Trials Networks. Our scientific agenda focuses exclusively on the RFA priority: "Prevention of HIV Infection".

The HIV Prevention Trial Network's (HPTN's) mission is to discover and develop interventions that can be used globally to prevent sexual or parenteral transmission of HIV. The HPTN methods integrate biomedical and technological advances with behavioral intervention strategies, and promoting substantive community involvement in culturally appropriate and contextually relevant ways. The future HPTN's priority areas for research to lower HIV transmission risk include (1) antiretroviral therapy (ART) for viral load reduction and consequent prevention of HIV transmission; (2) treatment of sexually transmitted infections (STI) to lower HIV transmission risk; (3) treatment of substance abuse and addiction, including injection drug use (IDU) and stimulants; and (4) behavioral risk reduction with HIV endpoints.

HPTN Prevention Research Can Have Rapid Global Impact

To date, no trial has demonstrated an effective human HIV vaccine or microbicide product. Both HIV vaccines and microbicides seek a successful "test of concept." Hence, these vital research areas are on a decades-long timetable before effective, safe, and affordable vaccine and microbicide products will be widely available for HIV prevention in the world's resource-limited settings. While ongoing, substantial investments in the discovery and development of these products are crucial, a balanced approach to research investment requires the identification of shorter-term, more immediate solutions to the global pandemic. The HPTN research agenda focuses on strategies of more immediate applicability in the fight against the HIV/AIDS pandemic making it unique among NIAID-sponsored HIV Networks in this prevention focus.

As the epidemic matures and access to ART increases globally, we will see a decline in HIV-related mortality, which is an urgent humanitarian imperative. Yet we will face new prevention challenges among those with established HIV infection, regardless of whether they receive ART or not. Treatment reduces mortality, but people who are infected and begin to feel better may continue or even increase high-risk behavior. Research is needed to optimize HIV care and ART use to lower transmission in developing countries, in the context of control of co-factors such as HSV-2 infection. It is this key role that the HPTN intends to fill: to advocate for and conduct the highest priority prevention trials that are likely to make the largest and most immediate impact on the pandemic.

Research Plan

The HPTN will focus on a prevention continuum from people who are uninfected to those with established infections. Three programmatic goals to prevent HIV transmission through targeted interventions will be directed at individuals and communities. These include:

- Testing interventions in high-risk uninfected individuals and communities to prevent acquisition of HIV infection
- Identifying and intervening with individuals with acute infection to prevent HIV transmission to others
- Evaluating the impact of antiviral agents and behavioral strategies in individuals with established HIV infection to prevent HIV transmission to others

These programmatic goals will be promulgated within Scientific Committees focused on antiretroviral therapy (ART), sexually transmitted infections (STI), and substance use (SU), and will be provided ethics, community, and behavioral/social science support.

HIV Prevention Continuum in the Third Decade of the Pandemic

HIGH-RISK, UNINFECTED INDIVIDUALS AND COMMUNITIES.

Although the HIV epidemic is continuing to spread, the vast majority of people in the world are still uninfected. Thus, it is imperative that new strategies be evaluated to reduce the risk of acquisition by HIV-negative individuals. The HPTN has four ongoing trials in HIV high-risk seronegative individuals that will transition to the new HPTN. These include evaluations of an STI control strategy, behavioral intervention, and two substance use strategies.

In addition to its ongoing trials, the HPTN proposes to evaluate the following approaches to reduce acquisition of HIV in high-risk HIV-uninfected populations:

- Improving vaginal health to prevent HIV in high-risk women
- Reducing risk of HIV acquisition in sexually active at-risk adolescent girls
- Testing the efficacy of community- and individual-based strategies aimed at reducing substance use (two trials focused on opiate and stimulant addiction, respectively)
- Assessing pre-exposure prophylaxis with ART

Improving vaginal health to prevent HIV in high-risk women

The current global consensus is that prompt treatment of bacterial STIs is an effective tool with which to reduce HIV transmission when the epidemic is not generalized. The effect of suppressing a viral STI on reducing risk of HIV acquisition is being evaluated in an ongoing study, HPTN 039, using acyclovir for HSV-2 in a randomized, placebo-controlled trial. It is not known whether treating vaginal infections (trichomoniasis, moniliasis, and bacterial vaginosis) and changing unhygienic vaginal behaviors will

reduce the risk of HIV acquisition. We believe this to be an essential prevention question. The plan is to start this trial in Year 1 of the award.

Specific Aims

1. To test the efficacy of periodic presumptive treatment of vaginal infections to prevent HIV transmission
2. To test the efficacy of a behavioral intervention to reduce high-risk intravaginal practices, including douching and re-use of contaminated cloths for menstrual hygiene

Reducing risk of HIV acquisition in sexually active at- risk adolescent girls

Adolescent girls and women are at the center of the African and Asian HIV epidemics. Sex with older men is the norm for many teens, and this conspires to introduce HIV infection shortly after coital debut. Little has been done to confront the particular circumstances of this age group in the world's most afflicted nations. This is proposed to commence in Year 2 of the award.

Specific Aims

1. To conduct a three-arm, clinic-randomized controlled trial to compare HIV infection rates in sexually experienced, at-risk adolescent and young women, comparing a standard HIV risk reduction counseling approach with two different interventions:
 - A behavioral intervention addressing gender and power relations delivered to the adolescent
 - A behavioral intervention addressing gender and power relations delivered to the adolescent and one or more of her sexual partner(s)
2. To assess the impact of the interventions on STI rates, unprotected intercourse, and number of sexual partners
3. To study the impact of the interventions on social norms regarding unprotected intercourse within the social and sexual networks

Simultaneous Application of Multiple HIV Prevention Programs to Reduce HIV Transmission Among Injecting Drug Users: a Structural Intervention

A major research gap in the HIV prevention arena is the absence of controlled studies to assess whether individual programs that work well can be combined and “scaled up” to effectively interrupt transmission at a community level. The HPTN proposes to engage this challenging area of research, with the expectation that National Institute for Drug Abuse will be interested in continuing its productive collaboration with HPTN and NIAID. This trial is planned to begin in Year 3 of the grant.

Specific Aims

1. To identify and engage communities with high HIV incidence due to IDU
2. To conduct a community-level randomized clinical trial of large scale implementation of a multifaceted program of substance abuse treatment and needle-related education to reduce HIV infection among IDUs
3. To assess secondary endpoints such as needle sharing, substance use frequency, impact of the program on primary prevention of substance abuse, and incidence rates of other blood-borne infectious agents (hepatitis B, hepatitis C, HTLV-I/II)

A Phase II Randomized Placebo Controlled Trial to Evaluate Modafinil Treatment of Cocaine Abuse in the Prevention of HIV-Related Risk

One of the most significant concerns of the 25-year-old link between substance abuse and HIV is the absence of proven effective prevention interventions for those who use cocaine, methamphetamine, and other amphetamine-type stimulants. Stimulant use among both heterosexual and MSM populations is increasing globally and has often been associated with both unsafe injection and heightened sexual risk behaviors after non-parenteral use. This trend in drug use may be responsible, in part, for accelerated HIV incidence rates among MSM in the United States, especially among younger men. In this research initiative, we plan to evaluate promising new pharmacotherapies, such as modafinil (Provigil™, Alertec™, Vigicer™) as new, vital tools for HIV prevention among stimulant-using populations. Our proposal is presented in expectation that NIDA will choose to continue its successful partnership with the HPTN and NIAID. This trial is planned to begin in Year 4 of the grant.

Specific Aims:

1. To test the “proof of concept” that modafinil pharmacotherapy (or a better medication available before the trial begins) is a promising adjunct to counseling for treatment of cocaine abuse. (We will seek analogous research opportunities as amphetamine pharmacotherapies become available)
2. To assess whether the use of modafinil (or other) pharmacotherapy is associated with reduced HIV risk behavior, and ultimately, HIV incidence. (Alternative pharmacotherapy options will also be considered.)

Assessing pre-exposure prophylaxis with ART

Researchers in the HIV prevention field have an intense interest in the promise of antiretroviral drugs to prevent HIV infection, when these drugs are taken before (pre-exposure prophylaxis or PREP) or after (post-exposure prophylaxis or PEP) sexual exposure. The practicality of this approach has been questioned, but we believe that there is a niche for PREP and PEP if they prove efficacious. In certain parts of the world, sexual risk is transient, as in the case of a rape victim (PEP candidate) or a woman entering the sex work field for a very short period of time, as is common in China (a PREP candidate). In the United States, MSM are turning toward these approaches, yet no one knows their efficacy. Microbicides are a form of PREP; it may be that an oral approach will be more feasible and/or more effective than a topical approach in the long run. We think our niche is best utilized in the second generation trials, after results from certain ongoing test-of-concept studies are available. Therefore, this study is planned to start in approximately Year 4 of the new Network.

Specific Aims

1. To test the efficacy of pre-exposure prophylaxis (PREP) with antiretroviral drugs to reduce HIV acquisition
2. To assess changes in behavior related to use of PREP as a prevention strategy, particularly whether or not other risk reduction approaches are reinforced or, perhaps, undermined, e.g., condom use, partner number

INDIVIDUALS WITH ACUTE/EARLY HIV INFECTION.

Individuals with acute infection are a critical link in the spread of HIV and the globalization of the pandemic. They harbor high viral loads that reach 10^3 to 10^7 viral copies/mL of plasma, yet they are unaware of their HIV status. Thus, they are oblivious to their own health status, and to the high risk they pose to others. Acutely infected individuals are most likely to transmit HIV efficiently³, particularly when they have coincident STIs. The HPTN leadership group has ranked interventions for individuals with acute HIV infection as a high priority for the prevention research agenda and will collaborate with the AACTG to pursue this agenda.

Specific Aims

1. To identify and recruit participants with acute/early HIV infection
 - a. To evaluate methods for detection of acute/early HIV infection
 - b. To evaluate clinical, biological and behavioral correlates of HIV transmission
2. To conduct a randomized trial to determine the effect of ART on HIV viral shedding, set point, CD4+ cell count, and sexual behavior

ESTABLISHED INFECTIONS; PREVENTING TRANSMISSION TO OTHERS.

Strategies using highly potent ART to reduce viral load among HIV-infected people may delay disease progression. HAART may have the added benefit of decreasing transmission, a principal focus of our research effort in the HPTN. Our ongoing HPTN 052 trial is evaluating ART in serodiscordant couples to prevent transmission and to determine whether treatment at an earlier stage of disease will ultimately prolong life. Since patients receive ART earlier (CD4+ cell count 300 – 500 cells/ μ L), HPTN scientists will be able to determine whether or not decreasing viral load will prevent transmission before patients progress to AIDS. Additionally, all patients are offered HAART once they reach CD4+ cell count <200 cells/ μ L or develop an AIDS-defining illness which enables an assessment of the impact of early versus late therapy on disease progression when compared to those people enrolled into the partner ACTG 5175 protocol. To extend and expand our work in this vital area, we propose two approaches and a trial for each. We will collaborate with the AACTG to demonstrate the efficacy of strategies to reduce HIV-risk behavior in infected individuals.

Specific Aims

1. To conduct studies of risk reduction with HIV-infected individuals to demonstrate the efficacy of strategies to reduce HIV-risk behavior
2. To conduct HIV prevention trials using treatment or prophylaxis of co-infections to reduce viral load in individuals with established HIV infection to demonstrate the efficacy of strategies to slow HIV-1 disease progression and to decrease HIV-1 genital shedding / infectivity

ORGANIZATIONAL STRUCTURE AND FUNCTION OF THE HPTN

The HPTN will be comprised of the following:

- Coordinating and Operations Center (CORE); PI: Sten H. Vermund; Family Health International (FHI)
- Network Laboratory Structure (NL); PI: Susan H. Eshleman; Johns Hopkins University (JHU)
- Statistical and Data Management Center (SDMC); PI: Thomas R. Fleming; Fred Hutchinson Cancer Research Center (FHCRC)

Partner institutions in the HPTN Leadership Group

The HPTN Leadership Group consists of a partnership between FHI, JHU, and FHCRC (Figure A). We have 19 other institutional partners among our leaders, such as Vanderbilt University, where Dr. Vermund is based. We will incorporate representative site leaders and NIH leaders in the leadership group, once sites are identified.

The Partners: Accountability within the HPTN Leadership

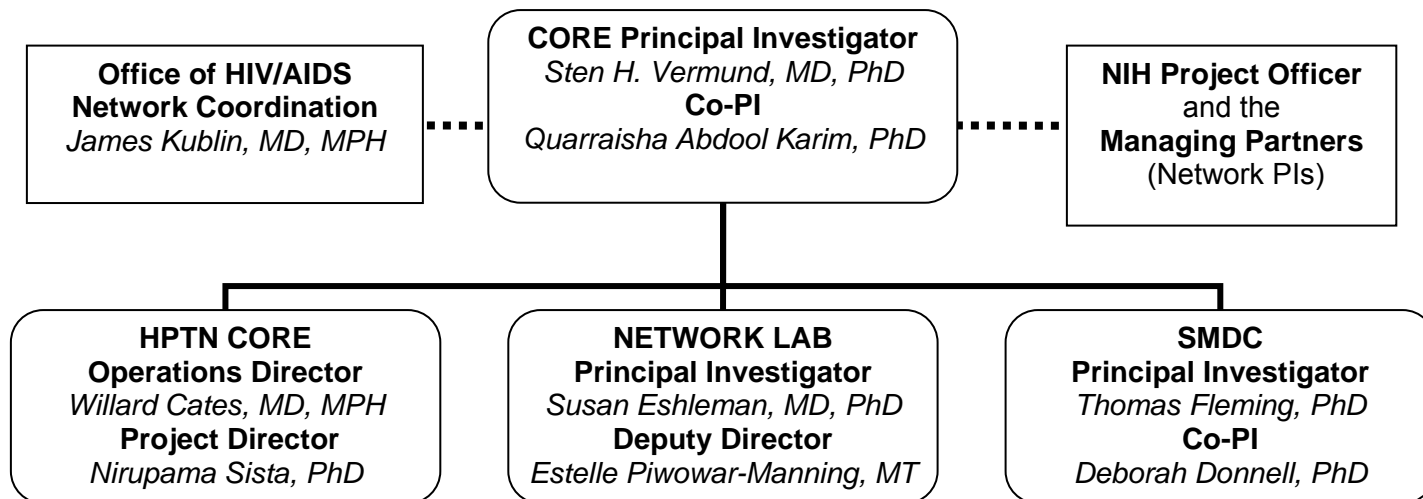


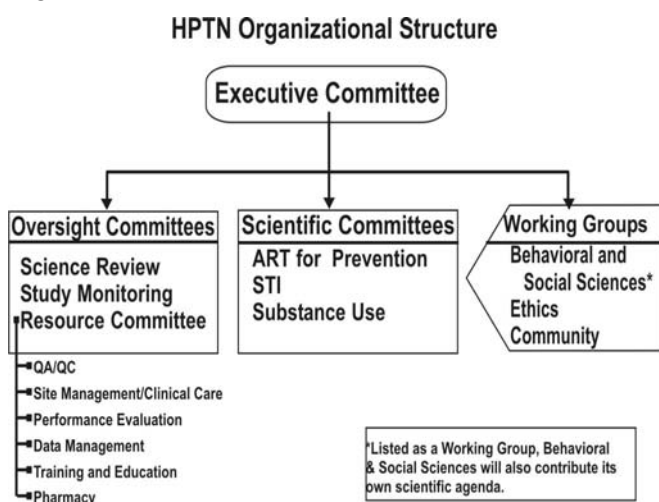
Figure A. HPTN leadership partners: individuals who are accountable for Network governance, function, integrity, and success, working through the Executive Committee (internal, outlined below) and the Managing Partners (external, as described in the RFA). The collaborating Clinical Trial Units will be engaged as soon as they are selected by NIAID and their other NIH partner institutes and centers.

Key Committees and Working Groups Within HPTN

The HPTN Leadership Group will govern the Network with the help of Scientific and Operational Committees, subcommittees, and Working Groups (Figure B). Each committee described in the RFA has a counterpart in our Network structure, making it easier for us to work with other DAIDS-sponsored Networks to harmonize operating

procedures. Consultative decisions will be made, in part, through committees and teams outlined in the RFA, as we have crafted specifically for the HPTN.

Figure B The Relationship of the EC to the Committees, Working Groups and Teams



We have Scientific Committees, cross-cutting Working Groups, and Resource Teams to serve as the Network units for collaboration, communication, science development, and trials management.

Our operations are organized to ensure good governance, streamlined science generation and review, and prompt initiation and efficient conduct of protocols. We will ensure that scientific priorities

are current and timely, and that studies are initiated and implemented in compliance with DAIDS policies. This includes state-of-the-art ethical and regulatory oversight and compliance. We will continue the process of building human capacity at trial sites, both among staff and for meaningful participation in research by communities and study volunteers. We are experienced with the adequate procurement, storage, and accountability of investigational new drugs. We are also experienced with budget planning and discipline. Finally, we are highly sensitive to the high demands of regulatory-standard trials in resource-limited settings.

EXECUTIVE COMMITTEE (EC)

The principal members of the HPTN leadership have an extraordinary array of experience and scientific integrity (Table A). We believe that our team of leaders, from seven nations and four continents, will have the breadth and depth of experience to manage the science and logistics of this Network. Furthermore, we share an impatience to move HIV prevention science forward, a vital characteristic for endeavors of this global magnitude. We are also pleased with the diversity of our leaders. Our team has excellent representation of minority, international, female, and/or younger investigators, a conscious decision on the part of the HPTN to nurture new talent and to seek diverse views on the prevention research agenda and its conduct.

The members of the EC (Table A) will serve as the main governing body of the HPTN Leadership Group and will be responsible for developing and implementing policy and procedures, adhering to timelines, and advising the NIAID about resource allocation. We composed the EC as per the RFA guidelines. The EC will be chaired by the HPTN PI, Sten Vermund and co-chaired by the HPTN CORE co-PI, Quarraisha Abdool Karim and will convene at least monthly.

- Sten H. Vermund, CORE Principal Investigator (PI), FHI and Vanderbilt University
- Quarraisha Abdool Karim, CORE co-PI Columbia University & CAPRISA**
- Willard (Ward) Cates, Jr, CORE Operations Director, Family Health International
- Susan Eshleman NL PI and director, Virology Core, Johns Hopkins University*
- Thomas Fleming, SDMC PI and Study Monitoring Committee Chair, University of Washington and Fred Hutchinson Cancer Research Center (FHCRC)
- DAIDS Staff Member
- Representative of NIH Consortium (if funding from other sources)
- HPTN Investigators (2)
- Community Liaison

* Minority, female, or international investigators. **Any two of these features.

Table A. Executive Committee, constructed as per RFA guidelines

SCIENTIFIC COMMITTEES AND WORKING GROUPS

Our science generation process will be nurtured through Scientific Committees and Working Groups in each of our strategic scientific areas of focus. The chairs and co-chairs are global leaders in HIV prevention research. We propose three Scientific Committees and three cross-cutting Working Groups. The Working Groups will provide considerable consultative support to the HPTN Scientific Committees and will also serve as a resource to other Networks that wish to take advantage of the HPTN's broad experience in behavioral sciences, ethics, and community work internationally and in the United States.

Collaborations across Networks will also be nurtured, when appropriate. Cross-cutting ideas will be vetted and scientific priorities set through joint meetings of the groups and, ultimately, at collective discussions of the scientific chairs at the EC level. They will join EC deliberations in an ad hoc capacity whenever Network scientific priorities are discussed. We now present briefly the charges of the Scientific Committees and Working Groups:

ART for Prevention Committee: Headed by Drs. Myron Cohen and James Hakim (Zimbabwe) from the HPTN, this committee is a joint activity with the AACTG. Dr. Susan Little of UCSD serves as a co-chair representing the AACTG. The committee will focus on such trials as HPTN 052, PREP studies, and on trials related to acute infection.

STI Committee: Headed by Drs. King Holmes and Patricia Garcia (Peru), this committee will continue to support HPTN 039, as well as new HPTN trials, e.g., for vaginal treatment and hygiene promotion for HIV prevention. This committee will develop the treatment and prophylaxis of co-infections protocol, an effort to reduce transmissibility by down-modulating HIV expression.

Substance Use Committee: Headed by Drs. David Vlahov and Apinun Aramrattana (Thailand), this committee will engage IDU risk reduction research and will develop new protocols to address the joint scourges of methamphetamines and cocaine use and their

associated high-risk sexual behaviors. HPTN 037 is ongoing and HPTN 058 will activate in 2005. HPTN 037 focuses on a network-based approach for risk reduction among IDUs. HPTN 058 uses buprenorphine/naloxone as an opiate agonist to treat heroin addiction and, in turn, reduce HIV transmission.

Behavioral and Social Sciences Working Group: Headed by Drs. Thomas Coates and Gina Wingood, this Working Group spearheads the current HPTN 043 trial of community level interventions to encourage VCT in high prevalence communities. A new protocol focused on adolescent interventions is presented in the grant. This committee will also provide behavioral science input for selected protocols in the HVTN, AACTG, IMPAACT, and MTN (see letters from Network leaders in section H).

Ethics Working Group: Headed by Drs. Jeremy Sugarman and Joseph Mfutso-Bengo (Malawi), this committee has produced ethics guidance documents (published in the *BMJ* in 2003) for scientists working in developing countries. They will promulgate more dialogue between the investigators and their constituents, and within the protocol teams, to anticipate and address key ethics challenges.

Community Working Group: Headed by Drs. Janet Fröhlich (South Africa) and LaHoma Smith-Romocki, this group will provide protocol and site-level assistance on issues of informed consent, community sensibilities, and research feasibility and logistics. We have a vibrant existing HPTN Community Working Group that has members from five continents, representing key constituencies in HIV prevention research. Although the RFA designates the community advisory board as a resource committee, we believe that their contribution to our Network is utilized more effectively at a Working Group level.

The Scientific Committees and Working Groups are the foundation for the HPTN's scientific creativity. We welcome site representation when CTUs are selected. Each chair and co-chair must manage the enterprise efficiently. Innovative and important concepts that are feasible and can shift prevention paradigms should be recognized and developed. Concepts that are redundant, are not cutting edge science, or are not feasibly conducted within the resource constraints will not move forward. We are pleased with the caliber and experience of the leaders who head our scientific development and review efforts.

SITE INVOLVEMENT: Since science development has its home within the Scientific Committees of the HPTN, we will recruit site investigators into our three Committees (ART, STI, Substance Use) and three Working Groups (Behavior, Ethics, Community), once sites are selected by the NIH. Site investigator and community perspectives are essential to mounting realistic, meaningful protocols as well as in proffering original research ideas. We anticipate successful integration with CTUs that have not been previously affiliated with the HPTN. We are also very optimistic that we can coordinate site involvement with other HIV Networks. This has occurred successfully with the ART for Prevention Committee that merged in 2004 with the Prevention Committee of the AACTG. HPTN 052 and A5175 are well coordinated in this collaboration. We intend to continue working with our current HPTN colleagues, led by Drs. J.B. Jackson and S. Hillier, who are spearheading applications in PMTCT (IMPAACT) and microbicide (MTN) research. We are enthusiastic about the HIV vaccine mission of the HVTN headed by Dr. L. Corey. There is substantial interest in "positive prevention" collaboration within the competing INSIGHT Network headed by Dr. J. Neaton. Dr. Vermund has been an active

co-investigator in the Adolescent Trials Network (ATN) of NICHD and its antecedent REACH study since its inception, and we are confident of collaborative opportunities with the ATN for adolescent-focused research. Hence, coordination of studies at the CTU and site level should be smooth, with the active involvement of site investigators and communities themselves, coordinated through the managing partners and DAIDS/NIAID.

SCIENCE OVERSIGHT COMMITTEES AND OPERATIONAL SUBCOMMITTEES

Science Review Committee (Kenneth Mayer, Helen Rees, Co-Chairs)

Once concepts or protocols move beyond the Scientific Committees and the EC, they will be reviewed for internal quality control by the HPTN Science Review Committee before being vetted at the NIH level by the NIAID Prevention Sciences Review Committee (PSRC), which may also seek input from collaborating Institutes such as NIDA, NIMH, or NIAAA. This final NIH review is mandated by NIAID to ensure full support of concepts to be funded within the cooperative agreement. Concepts can be proposed from outside of our leadership group as well; the incumbent HPTN Network has ongoing protocols that are lead by such outside investigators, e.g., HPTN 037 Protocol Chair Dr. Carl Latkin. As described in the RFA, a managing partners group, comprised of the PIs of the key HIV/AIDS Networks, will advise the NIH on research priorities for funding support. A subgroup of this committee will focus on manuscript review and feedback to authors before submission. This has been an excellent vehicle for quality assurance, much appreciated by the authors and the NIAID, in the present HPTN. Thomas Coates, Thomas Fleming, Helen Rees, and Kenneth Schulz are members of the manuscript subgroup.

Study Monitoring Committee (Thomas Fleming, Chair)

This committee provides feedback to the site investigators, the EC, and the NIH during the conduct of trials, hence serving as an “early warning system” of progress or problems in trial conduct. The Study Monitoring Committee has been a vital contributor to the current Network, resulting in addition or deletion of sites, innovation in recruitment and/or retention, and other critical mid-course adjustments to improve data quality or to otherwise maximize the success of trials.

Resource Committee (Nirupama Sista, Chair)

This committee and its six operational teams focus on facilitation of studies and their oversight. Study management is facilitated by smaller teams, largely staffed by FHI and SCHARP. The operational teams are presented in detail in the CORE proposal:

- Quality Assurance/Quality Control (Chaired by Michelle Immelman, FHI)
- Site Management and Clinical Care (Chaired by Melissa Allen, FHI)
- Performance Evaluation (Chaired by Nirupama Sista, FHI)
- Data Management (Chaired by Deborah Donnell, SCHARP/FHCRC)
- Training and Education (Chaired by Robert Bollinger, JHU)
- Pharmacy (Co-Chaired by Mauro Schechter, Hospital Univ. C.F.F. and Michelle Immelman, FHI)

We have formed these teams within our existing Network in an effort to contribute to the important work of Dr. James Kublin and his Office of HIV/AIDS Network Coordination in synergizing common procedures across NIAID Networks. Dr. Kublin will work closely with us, as he has since 2004, to ensure that we harmonize key training, laboratory, Network evaluation, data management, and other key functions with our sister NIAID HIV Networks. We are fully committed to this effort, which should achieve economies of effort and resources. It may also improve the quality of the science and the ability for Networks to support each others work in an environment where sites are pleuripotential rather than linked to only one Network.

Dr. Immelman will be responsible for regulatory affairs in HPTN. Since regulatory issues arise notably on both the Quality Assurance /Quality Control (QA/QC) Team and the Pharmacy Team, Dr. Immelman chairs one and co-chairs the other committee. She will improve communications with, and responsiveness of, OPCRO/DAIDS/NIAID, working closely with two physician employees, the Protocol Chairs, and Dr. Vermund.

PARTNER INSTITUTIONS

Coordinating and Research Operations Center (CORE)

The CORE is responsible for providing oversight of all operational and scientific aspects relating to science implementation of ongoing and proposed trials. In addition, the CORE will provide the HPTN secretariat, financial management/budgeting, and communications and coordination support to the HPTN leadership and site investigators. Key personnel in the CORE are Drs. Vermund (CORE and HPTN PI), Willard Cates, Jr. (CORE Operations Director), and Nirupama Sista (CORE Project Director). A major benefit to the HPTN is the proposed involvement of the CORE with two other prevention-oriented Networks (MTN and IMPAACT). The ongoing international perinatal trials will be completed by FHI. This will enable all networks to benefit from the experiences of the others.

Network Laboratory (NL)

Oversight and coordination of the laboratory services required for the proposed scientific agenda will be provided by the HPTN NL at the JHU School of Medicine. The PI for the NL is Susan Eshleman, MD, PhD, and the deputy director is Estelle Piwowar-Manning, MT-ASCP (SI). The HPTN NL is fully centralized with five Laboratory Cores: Virology, STI/Microbiology, Pharmacology, Toxicology, and Immunology at JHU. The NL is centered in the Department of Pathology at the JHU SOM and has the full support of the department and its chairman, J. Brooks Jackson (current HPTN CL PI). The NL is also supported by the department's Informatics Division and its Office of Continuous Quality Improvement. The NL includes four full-service CLIA-certified clinical laboratories that serve Johns Hopkins Hospital (the HIV Specialty Lab, Clinical Virology Lab, Microbiology Lab and Toxicology Lab). These are complemented by six renowned laboratories which specialize in assays related to HIV and its prevention that are either CLIA-certified or operate under GCLP standards: The HIV Genotyping Lab, STI Lab, Analytic Lab, Drug Development Lab, Flow Cytometry Lab and Immunology Lab. Dr. J. Brooks Jackson will continue to serve the HPTN NL as co-director of QA/QC Core, and will be PI of the proposed IMPAACT Network for PMTCT and pediatric HIV trials. We will benefit from his enormous experience. His role in IMPAACT will facilitate collaborations between the HPTN and IMPAACT Networks.

Statistical and Data Management Centre (SDMC)

The Statistical Center for HIV/AIDS Research in Prevention (SCHARP) is based at the Fred Hutchinson Cancer Research Center (FHCRC). In partnership with the University of Washington, SCHARP/FHCRC will serve as the SDMC. The SDMC will provide biostatistical leadership and central data management capabilities for the HPTN research. . As the incumbent SDMC in the HPTN, this experienced team (Table B) is familiar with site capabilities and establishing the information technology infrastructures needed to ensure data integrity and efficient transfer of data from site to SDMC. They are also responsible for many QA/QC and training functions in the Network. SDMC staff are leaders in protocol design, study oversight, data analysis, and manuscript preparation.

A major benefit to the HPTN is the proposed involvement of the SDMC with two other prevention-oriented Networks (HVTN, MTN) such that prevention sciences data management are coordinated and synergized within a single grantee. Since this has been the case for the HVTN and the HPTN already, both Networks benefit from the experiences of the other. Thomas Fleming, PhD, has served as the director of the HPTN Statistical Center since 1999 and is proposed to continue this role as PI of the SDMC.

SPECIAL FEATURES OF THIS NETWORK

RESEARCH TO PRACTICE IN THE HPTN

The NIH “Roadmap” emphasizes the need to produce “deliverables” for the American taxpayer from the investments they make through groups like the NIAID HIV/AIDS Networks. The HPTN focuses on research that has the shortest time frame for research results to become relevant for global public health or clinical application. We are committed to moving our Network research agenda forward in a timely, accountable way. To illustrate the specifics of the current and proposed HPTN research agenda, we frame our research priorities and activities in the context of global HIV prevention research activities, and describe how we collaborate with sister NIH-sponsored Networks and with independently funded prevention researchers.

The leaders assembled for this proposal urge the NIAID to pursue prevention options that, if successful, are immediately available for scale-up in the global battle against HIV. An example of the HPTN’s success in rapidly implemented “research-to-practice” is the HIVNET 012. Within only a few months of the 1999 Lancet publication by HPTN investigators, the Elizabeth Glaser Pediatric AIDS Foundation “Call to Action” program was announced, co-sponsored by the Bill and Melinda Gates Foundation and, later, by the U.S. Agency for International Development and the CDC Global AIDS Program. Tens of thousands of infant lives have been saved in the world’s poorest nations through “Call to Action” and its sister programs. An example of an HPTN trial with this kind of potential immediate impact is the ongoing HPTN 039 trial, which tests whether suppression of HSV-2 with acyclovir prevents HIV transmission. The widespread availability of inexpensive suppressive therapy for genital herpes could promote the diagnosis and suppressive treatment of HSV-2 infection in nations with high HIV incidence and HSV-2 prevalence rates. We believe that our work is complementary to efforts in microbicide and vaccine discovery that may make a major impact, but not for many years to come. HPTN research offers the potential to find practical strategies for HIV prevention that can be applied quickly.

The target populations for our primary research agenda will be high-risk individuals and high-incidence regions. In the PEPFAR and Global Fund era, what is the role for HIV prevention linked to care for HIV-infected individuals? Low ART drug prices make it easier to treat HIV even in resource-limited settings, so why does the prevention agenda remain so critical? It is the view of this Leadership Group that therapy that falls short of curing HIV infection will never rid the world of the HIV pandemic. We recognize that HIV treatment is a vital adjunct to prevention; it is a humanitarian imperative, and we highlight the HIV-infected person in much of our research agenda. However, no one should forget the primacy of the HIV prevention agenda globally for humanitarian reasons and for cost-containment. In the next few years, millions of HIV-infected individuals in developing countries will likely have access to ART. This generates a huge prevention opportunity. Can ART be targeted to those with acute infection such that their infectiousness can be modified to decrease transmission to others? Can we incorporate effective risk reduction messages into the clinical care environment to reduce new infections? Can individuals not yet on ART benefit from aggressive management of co-infections, and can this reduce their infectiousness? We are committed to an integrated vision of care and prevention in HIV/AIDS research, and we look forward to working closely with the ACTG and INSIGHT Networks, if they and we are funded.

COMMITMENT TO COMMUNITY AND INTERNATIONAL SITES

The HPTN is well known for its commitment to community consultation and involvement, linked to protocol development, site management, and dissemination. Communities partner with investigators in education, advocacy, and oversight. Our ethics team of HPTN, working hand-in-hand with the community and behavioral teams, provides assertive input at every level of protocol development. It is a credit to the HPTN that our behavioral scientists and ethicists are seen as assets to other NIAID-sponsored Networks, as documented in our letters of agreement. HIVNET and HPTN leadership has built partnerships and infrastructures with the NIH over the past 11 years. These efforts have helped to prepare NIAID for the wide variety of international research studies in prevention, vaccines, microbicides, and therapy proposed by Networks responding to this RFA.